PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	**CELAL ALBAYRAK**	**Examiner:**	**MAURY A. AUDET**
Serial No.:	**10/506,952**	**Group Art Unit:**	**1654**
Filed:	**September 8, 2004**		
For:	**MICROPARTICLES AND METHOD FOR THEIR PRODUCTION**	**Docket No.**	**ABS0006/US**

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Commissioner for Patents
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I CERTIFY THAT ON Jan 7, 2009, THIS CORRESPONDENCE IS BEING ELECTRONICALLY TRANSMITTED TO THE UNITED STATES PATENT AND TRADEMARK OFFICE VIA THE OFFICE'S EFS-WEB

DALE A. BJORKMAN

PRE- BRIEF CONFERENCE REQUEST

Dear Sir or Madam:

This communication is being filed with a Notice of Appeal.

It is believed that no other fee is required in filing this submission. However, if any fee is required, please charge the appropriate fee to the Kagan Binder Deposit Account No. 50-1775 and notify us of the same.

PRE-BRIEF CONFERENCE REQUEST

Claims 1 and 3-9 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Hutchinson (US 5,889,110) in view of Chen et al (US 7,081,489), Bhagwatwar et al (US 2003/0049320) and Yeh et al (US 5,869,103), cited by the International Authority in related PCT Search Report.

It is respectfully submitted that the above rejection is based on a fundamental misinterpretation of the primary reference, Hutchinson, and also on a misinterpretation of the secondary reference to Chen.

The present invention provides a method for the preparation of nano- or microparticles, wherein an active substance is embedded in a polymer matrix by precipitating the active substance in a solution containing the polymer, and subsequently solidifying the polymer. The method is different from prior art techniques, because instead of adding the active substance in a solid state to the polymer solution, the active substance particles are formed in situ in the polymer solution by manipulation of solvents. This precipitation and particle formation of the active substance takes place in a solution wherein the polymer is still dissolved in an organic solvent. The polymer is only then solidified to form the suspension of nano- or microparticles containing the precipitated active substance.

As stated in present claim 1, the present invention comprises the steps of:

a) combining a solution of an active substance dissolved in a smaller amount of a first solvent L1 with a solution of a polymer in a larger amount of a second organic solvent L2, said solvent L2 dissolving the polymer but being a non-solvent for the active substance, thereby effecting precipitation of the active substance in a solution which comprises the polymer dissolved in an organic solvent to obtain a suspension of the active substance, and

b) mixing the obtained suspension with an aqueous surfactant solution and solidifying the polymer to obtain a suspension of nano- or microparticles which contain an active substance.

Thus, the present claims require solvents L1 and L2 to be mixed together. The mixture of these solvents is a fundamental basis of how the present invention operates.

This in-situ precipitation by addition of a non-solvent for the active agent to a solution containing both the active agent and the polymer is significant in providing a gentle and efficient precipitation process, and provides advantages that cannot be achieved by the prior art methods. Advantages to the present process whereby the active substance is precipitated in a solution environment without drying are discussed in more detail in the Response filed April 11, 2008 at pages 2-3 of the Response.

In contrast, Hutchinson does not permit mixing of the two solvents discussed in his process, because he freeze-dries the active ingredient and adds it to the second solvent in dry form (Claim 16, step iv).

Hutchinson discloses salts composed of a cation derived from a peptide containing at least one basic group and an anion derived from a carboxy-terminated polyester, processes for the manufacture of such salts, and the use of such salts in the manufacture of extended release pharmaceutical compositions (i.e. microparticles). See the Abstract. The process of making such microparticles is detailed, for example, in claim 16, which states:

> 16. Microparticles comprising a composition consisting essentially of a salt formed from a cation derived from a peptide containing one or more basic groups and an anion derived from a carboxy-terminated polyester, which composition has been prepared from at least an approximately stoichiometric equivalent of said polyester carboxylic acid end groups relative to said basic peptide groups, obtainable by a process comprising
>
> i) dissolving the basic peptide and carboxy-terminated polyester in a first solvent in which both the peptide and the polyester are soluble to form a first solution;
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> ii) freezing said first solution at high speed to form a frozen mixture;
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> iii) freeze-drying the frozen mixture to remove said first solvent, forming a freeze-dried product;
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> iv) dispersing the freeze-dried product into a second solvent which is a solvent for the polyester and a non-solvent for the peptide to form a second solution containing said peptide/polyester salt; and

> v) removing said second solvent from said second solution by a procedure selected from the group consisting of spray-drying, spray-congealing, evaporation and phase separation coacervation to form a solid product which is in the form of microparticles, or from which said microparticles are thereafter formed.

(emphasis provided)

Note that the first solvent and the second solvent of Hutchinson are never together in the same solution. The first solvent is removed in step iii) before the second solvent is introduced in step iv). In particular, there is no precipitation of the active agent caused by the action of a non-solvent for the active agent (L2), as required by the present claims. Rather, the solidification both in steps iii) and v) is effected via conventional ways of solvent removal. Thus, it is impossible for Hutchinson to carry out an essential step of the presently claimed method.

However, the Final Rejection at page 4 states "It is clear Hutchinson teach L1/L2, wherein the latter is increased, following a precipitation step, and wherein the L2 is a non-solvent to the goserelin acetate (see e.g. claim 16, step iv)." This interpretation of Hutchinson to ever have a composition comprising both L1 and L2 is clear error in view of the foregoing.

It is respectfully submitted that the final rejection is predicated on an incorrect reading or understanding of the primary reference. Further, this error is fatal to the viability of the rejection. The rejection therefore should be withdrawn.

The Final Rejection goes on to state that Chen is cited to remedy the deficiency that the combination of references does not teach the precipitation of the active substance prior to solidification. See page 3 of the Final Rejection. [Note that only the subject matter disclosed in the provisional patent application of Chen may be cited against the present application. See the Response filed April 11, 2008 at page 5.]

However, neither the Chen Patent nor the provisional application to which it claims priority discloses addition of the active substance to the polymer solution in a form other than the solid state. Thus, Chen provides no teaching with respect to precipitation of an

active substance as set forth in the present claims, and cannot remedy the deficiency identified in the Final Office Action.

It is respectfully submitted that the final rejection therefore further errs in the reading or understanding of the secondary reference to Chen by asserting that this reference, which only provides the active ingredient in the solid state, could provide a teaching with respect to precipitation of an active ingredient. It is respectfully submitted that this rejection should be withdrawn for this reason as well.

The other references of record similarly do not provide a teaching or suggestion of in-situ precipitation of an active agent in a polymer solution prior to its encapsulation in a polymer. Specifically, Bhagwatwar does not contemplate precipitation of the active ingredient, but rather provides delivery of solvated drugs in a gelled polymer droplet-in-oil dispersion. Likewise, Yeh does not contemplate precipitation of the active ingredient. See the discussion of these references at pages 5 and 6 of the Response filed April 11, 2008.

Thus, even in combination, the properly interpreted references teach the skilled artisan to add the active substance to the polymer solution in dry form.

CONCLUSION

It is respectfully submitted that the outstanding rejection on the record if formulated on a misinterpretation of the Hutchinson and Chen references. Because this basis of rejection is clearly in error, a favorable decision by the Conference Panel is appropriate in this case and is hereby requested. In the event that a phone conference between any member of the Conference Panel and the Applicants' undersigned attorney would help resolve any remaining issues in the application, the Examiner is invited to contact the attorney at (651) 275-9811.

Dated: January 7, 2009

Respectfully Submitted,

By: _____

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